PERIODONTAL DISEASE AND PREGNANCY OUTCOMES:

STATE-OF-THE-SCIENCE

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This review is built and expanded upon the findings of a previously published systematic review article (*Xiong et al. Periodontal disease and adverse pregnancy outcome: a systematic review. BJOG 2006;113:135-143*). This updated review includes 19 new studies published from March 2005 to date. This review was supported in part by the federal Health Resources and Services Administration, Maternal and Child Health Bureau.

SUMMARY

Background and Objectives
Recent studies suggest that periodontal disease, as a source of sub-clinical and persistent infection, may induce systemic inflammatory responses that increase the risk of adverse pregnancy outcomes. The objective of this paper is to synthesize the current evidence on the relationship between periodontal disease and adverse pregnancy outcomes.

Methods
Literature search strategy We identified studies published in peer-reviewed journals via searches of the MEDLINE, EMBASE, CINAHL, and Current Contents full-text databases.

Study inclusion criteria We selected observational studies (i.e., case-control, cross-sectional and cohort) and non-randomized controlled studies or randomized controlled trials that examined periodontal disease as a risk factor for adverse pregnancy outcomes.

Data extraction We extracted Odds ratios (OR) or risk ratios (RR), or ORs/RRs were calculated from the studies' data.

Statistical pooling We calculated pooled effect size for the clinical trials. We did not pool the effect sizes for the observational studies due to the heterogeneity in definitions for periodontal disease and adverse pregnancy outcomes across studies.

Results
Forty-four studies (26 case-control, 13 cohort, and 5 controlled trials) were identified. The studies focused on preterm low birth weight, low birth weight, preterm birth, birth weight by gestational age, miscarriage or pregnancy loss, pre-eclampsia, and gestational diabetes mellitus. Of the chosen studies, 29 suggested an association between periodontal disease and increased risk of adverse pregnancy outcome (ORs ranging from 1.10 to 20.0) and 15 found no evidence of an association (ORs ranging from 0.78 to 2.54). A meta-analysis of the clinical trials suggested that oral prophylaxis and periodontal treatment may reduce the rate of preterm low birth weight (pooled RR: 0.53, 95% confidence interval (CI): 0.30-0.95, $p<0.05$), but did not significantly reduce the rates of preterm birth (pooled RR: 0.79, 95% CI: 0.55-1.11, $p>0.05$) and low birth weight (pooled RR: 0.86; 95% CI: 0.58-1.29, $p>0.05$).

Conclusions
Periodontal disease may be associated with an increased risk of adverse pregnancy outcome. However, more methodologically rigorous studies are needed for confirmation.

INTRODUCTION

Periodontal disease. Periodontal disease is one of the most common chronic disorders of infectious origin known in humans, with a reported prevalence varying between 10 and 90% in adults, depending on diagnostic criteria.[1-5] Periodontal disease presents as two main types (see Figure 1): [6]

- Gingivitis—an inflammatory condition of the soft tissues surrounding a tooth or the gingiva; and

- Periodontitis—involving the destruction of such supporting structures as the periodontal ligament, bone, cementum or soft tissues.

Gingivitis does not affect the supporting structures of teeth, is often caused by inadequate oral hygiene, and is reversible with professional treatment and good oral home care. Untreated gingivitis can advance to periodontitis, which results in loss of connective tissue and bone support and is a leading cause of tooth loss.[5, 6] In general, periodontal disease is initiated by overgrowth of certain bacterial species, with a majority of gram-negative, anaerobic bacteria growing in subgingival sites. The host response to periodontal pathogens causes persistent inflammation and the destruction of periodontal tissues that support teeth,[6, 7] leading to clinical manifestations of disease.

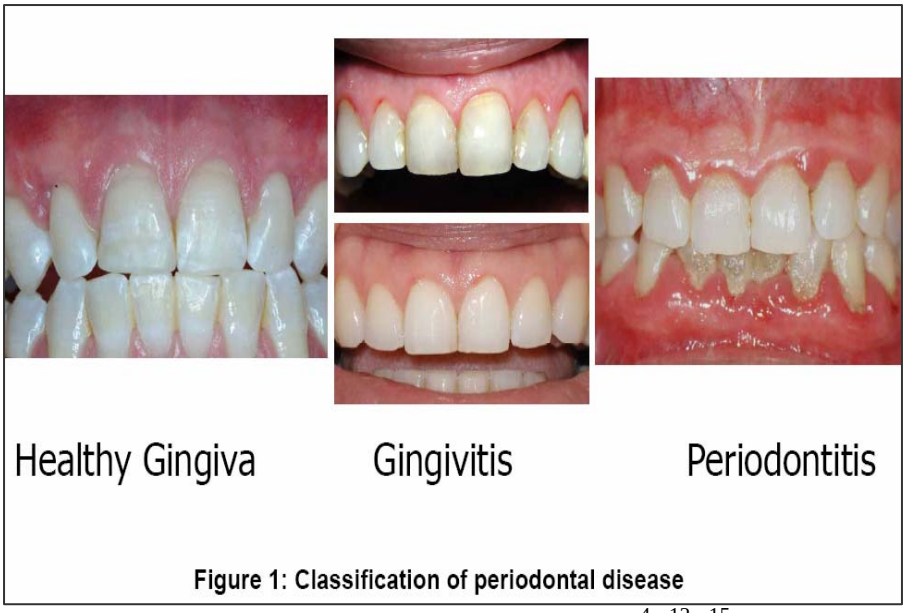

Figure 1: Classification of periodontal disease

Periodontal disease and systemic diseases. The past ten years have witnessed an increase in research evidence suggesting associations between periodontal disease and increased risk of systemic diseases such as atherosclerosis, myocardial infarction, stroke, diabetes mellitus, and adverse pregnancy outcomes.[8-12] Since Offenbacher et al.[8] first reported an association between periodontal disease and preterm low birth in 1996, adverse pregnancy outcomes that have been linked to periodontal disease include preterm birth, low birth weight, miscarriage or early pregnancy loss and pre-eclampsia.[12] Pre-eclampsia and preterm births are major causes of maternal and perinatal morbidity and mortality.[13, 14]

Public health importance. Studies have shown that periodontal disease can affect about 20% to up to 50% of pregnant women, especially economically disadvantaged (e.g., African-American) women.[4, 12, 15] Because periodontal disease is so prevalent among pregnant women, any adverse effect it may have on pregnancy outcomes would have a great public health impact. In addition, the specific etiologies and pathogeneses of these adverse pregnancy outcomes mentioned above are still unclear; few risk factors have been clearly identified as early predictors or modifiable risk factors for purposes of determining intervention strategies. A confirmation of periodontal disease as an independent risk factor for adverse pregnancy outcomes would be of great public health importance, because periodontal disease is both preventable and curable. Improving periodontal health before or during pregnancy may prevent or reduce occurrences of these adverse pregnancy outcomes and therefore reduce maternal and perinatal morbidity and mortality.

The objectives of this review are to synthesize the existing literature, to discuss methodological issues and potential biases among existing studies, and to consider underlying biological mechanisms for reported associations.

METHODS

Literature search. We searched for studies in four computerized databases: MEDLINE, EMBASE, CINAHL, and Current Contents (January 1966 to August 2006). Our primary search terms were *periodontal disease(s)*, *gingivitis*, and *periodontitis*, cross-referenced with *gestational age*, *birth weight*, *preterm birth or delivery*, *premature birth or delivery*, *low birth weight*, *pregnancy*, *pregnancy loss*, *fetal growth restriction*, *small-for-gestational age*, *miscarriage*, *abortion*, *pre-eclampsia or eclampsia*, *hypertension*, or *pregnancy-induced hypertension*, *gestational diabetes*, *or gestational diabetes mellitus*. Studies were also located by reviewing reference lists and bibliographies in selected articles.

Study inclusion criteria. We used the following criteria for study selection:

1) They were comparative studies (i.e., case-control, cross-sectional, cohort, or non-randomized controlled studies or randomized controlled trials) of pregnant women;

2) Periodontal disease was defined by at least one of several *clinical* periodontal indices; and

3) The pregnancy outcomes were preterm birth, low birth weight, gestational age, small-for-gestational age, birth weight, pregnancy loss or miscarriage, gestational diabetes, or pre-eclampsia.

Data extraction. A form designed a priori was used to extract the information from the selected studies. We extracted odds ratios (OR) and risk ratios (RR) from the selected studies, along with other study characteristics (e.g., sample size, definitions of periodontal disease, information on confounders being controlled) and study conclusion(s). Some studies did not provide ORs or RRs, so the ORs or RRs were calculated from the studies' data. Some studies did not provide sufficient information for effect size estimates (i.e., ORs or RRs).

Study quality assessment. We did not assess the quality of the selected studies because of the differences in the definitions of periodontal disease and adverse pregnancy outcomes, as well as potential biases among the studies (see Discussion).

Statistical pooling/meta-analysis. For the observational studies (i.e., case-control or cohort studies), due to the high level of heterogeneity in periodontal disease and adverse pregnancy outcome definitions across studies, it was not appropriate to apply statistical methods to estimate overall pooled risks of periodontal disease. Therefore, we used the "vote-counting" method for the observational studies in this review.

For the clinical trials,[16-19] we did apply statistical pooling to estimate overall RR. Pooled RR was obtained by weighting each study using the inverse of the variance of the RR's natural logarithm.[20] This variance was computed for each study from 95% RR confidence intervals; unreported confidence intervals were computed from distribution data. A fixed-effects model was used to pool RR, since heterogeneity tests were not statistically significant for a pooled analysis.[20, 21]

RESULTS

An overview of existing studies on this topic according to the study type is presented in Table 1-3 and Figure 2. Of the 44 selected studies, 26 were categorized as case-control

(including cross-sectional) (Table 1),[8, 22-44] 13 cohort (Table 2),[4, 45-56] and 5 controlled trials (one not randomized) (Table 3).[16-18, 57] The studies were conducted in 23 countries—13 USA; 4 UK; 3 Brazil; 2 Chile; 2 Turkey; 2 Canada; 2 Hungary; and 1 each Argentina, Austria, Brazil, Colombia, Croatia, Denmark, Germany, Iceland, Iran, Israel, Saudi Arabia, Senegal, Spain, Sri Lanka, Thailand, and Venezuela. Several cohort studies and clinical trials examined the relationship between periodontal disease and more than one pregnancy outcome. In all, 29 of the 44 studies suggested that periodontal disease is a risk factor for preterm low birth weight,[8, 16, 27, 46, 57] low birth weight,[4, 22-24, 33, 36, 37, 46, 53] preterm birth,[4, 18, 28, 29, 33, 42, 45, 46, 51, 58] very preterm birth,[54] pre-eclampsia,[30, 34, 43, 48] decreased birth weight and shortened gestational age,[4, 47] miscarriage or stillbirth,[49] small-for-gestational age or intrauterine growth restriction,[55] or gestational diabetes mellitus.[44] Fifteen studies (from Argentina, Brazil, Canada, Denmark, Germany, Iceland, Sri Lanka, Turkey, the UK and the USA) did not find that periodontal disease is a risk factor for preterm low birth weight,[25, 32, 35, 52] low birth weight,[19, 38, 40, 41, 49, 56] preterm birth,[19, 26, 31, 38, 39, 41, 49, 50, 56, 59] small-for-gestational age or intrauterine growth restriction,[19] or preeclampsia.[41]

Periodontal disease and preterm low birth weight. A summary of studies according to pregnancy outcome is shown in Table 4. Results from two case-control studies[8, 27] and one cohort study[46] suggest that periodontal disease is a risk factor for preterm low birth weight (with ORs and RRs ranging from 3.5 to 7.5 for the observational studies). Three clinical trials (one not randomized)[16, 17, 57] suggest that oral prophylaxis and treatment (e.g., scaling and root planing) can reduce the incidence of preterm low birth weight. Results from one trial whose participants were 164 economically disadvantaged African-American (60%) and Hispanic (39%) women living in the USA[16] showed that oral prophylaxis resulted in a 28% reduction in preterm low birth weights (RR: 0.72, 95% CI: 0.4-1.47, $p>0.05$). Results from the other trial, including 400 economically disadvantaged women living in Chile,[17] indicated that periodontal treatment led to an 82% reduction in preterm low birth weights (RR: 0.18, 95% CI: 0.05-0.60, $p<0.01$). The pooled RR from these two trials was 0.53 (95% CI: 0.30-0.95, and $p<0.05$), with a 47% reduction in preterm low birth weight incidence (Figure 2). In contrast, three case-control studies[25, 32, 35] and one cohort study[52] failed to identify a relationship between periodontal disease and preterm low birth weight. The studies conducted in the UK and Germany found that periodontal disease is actually associated with a decreased risk of preterm low birth weights.[25, 35]

Periodontal disease and preterm birth. Results from twelve studies (five case-control,[28, 29, 33, 42, 58] five cohort[4, 45, 46, 51, 54] and two trials[17, 18]) suggest that periodontal disease is a risk factor for preterm birth or very preterm birth (with ORs and RRs ranging from 2.12 to 20.0). Results from the trial in Chile[17] indicated that periodontal treatment led to an 81% reduction in preterm birth (RR: 0.19, 95% CI: 0.04-0.85, $p<0.01$). A pilot randomized controlled trial with a population consisting of 85% African-American women in the USA[18] indicated that providing scaling and root planing to pregnant women with periodontal disease may reduce preterm births < 37 weeks of gestation (RR: 0.5, 95% CI: 0.2-1.3, $p>0.05$) and very preterm birth < 35 weeks of gestation (RR: 0.2, 95% CI: 0.02-1.4, $p>0.05$). However, eleven studies (six case-control,[26, 31, 38, 39, 41, 59] four cohort [49, 50, 53, 56] and one trial[19]) failed to find the same

association. A recent NIH-funded multicenter randomized controlled trial of 823 pregnant women found that treatment of periodontal disease in pregnancy did not reduce rate of preterm birth (RR: 0.93, 95% CI: 0.58-1.29, p>0.05).[19] The pooled RR from these three trials[17-19] was 0.79 (95% CI: 0.55-1.11, p>0.05), indicating that periodontal treatment does not significantly reduce the rate of preterm birth (Figure 2).

Periodontal disease and low birth weight. Results from ten studies (six case-control,[22-24, 33, 36, 37] three cohort [4, 46, 53] and one trial[17]) suggest that periodontal disease is a risk factor for low birth weight (with ORs and RRs ranging from 1.1 to 7.2). However, five studies (two case-control,[38, 41] two cohort[49, 56] and one trial[19]) found no such association. The pooled RR from these two trials[17, 19] was 0.86 (95% CI: 0.58-1.29, p>0.05), indicating that periodontal treatment does not significantly reduce the rate of low birth weight (Figure 2).

Periodontal disease and miscarriage. Two British cohort studies that failed to find any association between periodontal disease and either preterm birth or low birth weight did suggest an association between periodontal disease and miscarriages or stillbirth (with RRs ranging between 2.53 and 3.84).[49, 56]

Periodontal disease and pre-eclampsia. Four studies (three case-control[30, 34, 43] and one cohort[48]) suggested an association between periodontal disease measured at delivery and pre-eclampsia (with ORs ranging between 2.4 to 3.47). However, one case-control study from Argentina found no association, with an adjusted OR: 0.99 (0.70-1.40).[41]

Periodontal disease and intrauterine growth restriction or small-for-gestational age. One research team studied the effect of periodontal disease on fetal growth and reported that periodontal disease was significantly associated with delivery of a small-for-gestational age infant, with an adjusted RR: 2.30 (1.10-4.50).[55] However, results from the NIH-funded multicenter clinical trial indicated that treatment of periodontal disease did not reduce the rate of small-for-gestational age infant (RR: 1.04, 95% CI: 0.68-1.58, p>0.05).[19]

Periodontal disease and gestational diabetes mellitus. One study based on the data from the third US National Health and Nutrition Examination Survey (NHANES III) found an association between periodontal disease and gestational diabetes mellitus, with an adjusted OR: 9.11 (1.11-74.9).[44]

Periodontal disease, birth weight, and gestational age. Results from one correlation analysis indicated an association between decreased average newborn birth weight or gestational age and greater severity of maternal periodontal disease.[47]

In summary, findings from observational studies yielded inconsistent conclusions on the relationship between periodontal disease and various pregnancy outcomes (Table 1 and Table 2). Of 39 observational studies, 25 (16 case-control and 9 cohort) suggested periodontal disease was associated with increased risk of adverse pregnancy outcomes. Among them, several studies demonstrated a dose-response relationship—that is, the risk of adverse pregnancy outcome increased as the severity of periodontal disease increased[4,23, 45, 60]—and periodontal disease was associated with even higher risk of very preterm birth (<32 weeks), birth weights below 1,500 g, and early pregnancy loss.[4, 26, 33, 45] Fourteen studies (ten case-control and four cohort) reported no associations. A meta-analysis of

the existing controlled trials suggested that treating periodontal disease during pregnancy may result in reduced risk of preterm low birth weight but did not significantly reduce the rate of preterm birth, low birth weight, or intrauterine growth restriction (Table 3 and Figure 2).

DISCUSSION

The majority of the studies, especially those carried out in economically disadvantaged populations, suggest that periodontal disease is associated with increased risk of various adverse pregnancy outcomes such as preterm birth and low birth weight. However, studies from European countries and Canada find no associations.

One difference was found in studies conducted in the USA or in developing countries and those conducted in European countries and Canada. The former tended to include African-Americans and women from economically disadvantaged families, and they consistently reported significant associations between periodontal disease and adverse pregnancy outcomes. In contrast, the studies conducted in European countries or Canada (all of which offer their citizens universal health care) did not find an association between periodontal disease and adverse pregnancy outcomes. This suggests that the effects of periodontal disease on adverse pregnancy outcomes may be different according to the socioeconomic status and access to dental care. The possible effects of modification of these conditions is worth further exploration.

Biological mechanisms. There is a large body of evidence pointing to infection as a key factor in adverse pregnancy outcomes.[61-65] Oral mechanical manipulation (e.g., tooth brushing, dental procedures, and even routine mastication) can cause bacteremia.[66] Chronic periodontal infections can produce local and systemic host responses leading to transient bacteremia. Lipopolysaccharide (LPS) endotoxins and other bacterial substances can gain access to gingival tissue, initiate and perpetuate local inflammatory reactions, and consequently produce high levels of proinflammatory cytokines. Such activations of maternal inflammatory cell responses and cytokine cascades play important roles in the pathophysiological processes of preterm labor, low birth weight, and pre-eclampsia.[9, 63, 65] In addition, LPS, bacteria from subgingival plaque, and proinflammatory cytokines from inflamed periodontal tissue can enter the bloodstream, reach the maternal-fetal interface, trigger or worsen maternal inflammatory response, and increase plasma levels of prostaglandin and cytokines (e.g., tumor necrosis factor).[9-11, 67] Thus, it appears that periodontal disease may play a nonspecific role in various adverse pregnancy outcomes.

Methodological Issues and Potential Biases

1. Periodontal Disease Definition

We noted several potential biases among the selected studies, with the most important being the great variation in periodontal disease definitions. Commonly accepted clinical measures of periodontal disease are clinical attachment level (CAL, the distance between the cemento-enamel junction and clinical pocket base) and probing depth (PD, the distance from the gingival margin to the apical part of the pocket), which were established 45 years ago.[68] Although various indices have been developed since then,[69, 70] most have limited validity.[71, 72] Because there is no universally accepted standard for periodontal disease diagnosis, most of the researchers used their own case definitions (mostly based on disease distribution within

the study population) that combined PD and CAL. Some studies defined periodontal disease in terms of Decayed, Missing, and Filled Teeth (DMFT) and Community Periodontal Index of Treatment Needs (CPITN) (Table 1), the Russell Periodontal Index (Table 2), and similar indices—all of which have limited sensitivity for disease detection.[70] We failed to find the same definition used in two or more studies, even by the same author(s) in different studies. Very few authors attempted to justify their criteria. Obviously, selecting different criteria to define periodontal disease will lead to different results.

2. Confounding effects

For those studies that reported an association, questions remain whether the observed associations represent a causal relationship or are due to the confounding effects of other variables such as low socioeconomic status and smoking.[11, 73] Although 29 of the 39 studies we reviewed (not including the five randomized trials) controlled for some confounding variables, the confounding variables that were included for adjustment vary greatly among studies. Several important confounding variables, such as previous histories of adverse pregnancy outcomes, infections (e.g., bacterial vaginosis and chorioamniontitis), antibiotic use during pregnancies, excessive body mass index, or maternal disorders (hypertension, diabetes), were not considered. Even though some of the studies adjusted for race, smoking, socioeconomic status and other important confounding variables by using multivariable regression analysis, it is possible that some residual confounding effects remain. For example, in a study of poor, rural, non-smoking Sri Lankan women, periodontal disease was not significantly associated with an increased risk of preterm low birth weight.[52] The author suggested that previously reported associations may have been due to the residual confounding effects of smoking and other variables, while also reporting that they were not adequately powered to test the association.[52]

3. Study Sample Size

Insufficient sample size is a concern for many of the studies (13 studies) that had fewer than 100 patients,[24, 27, 29, 30, 34, 35, 39, 42, 47, 50, 51, 53, 57] thus increasing the potential for associations observed by chance (random error) or lack of statistical power.

4. Pregnancy Outcome Definition

We also found considerable variation in definitions of adverse pregnancy outcomes. Many studies used "preterm low birth weight"—meaning low birth weight (<2,500 g) infants born preterm (<37 weeks). Others used such labels as "preterm *or* low birth weight" and "preterm *and/or* low birth weight." It is generally accepted that preterm births and low birth weights have distinct etiologies,[74, 75] so such definitions were somewhat confusing—in some situations apparently excluding preterm infants with normal birth weights and full-term infants with low birth weights (i.e., intrauterine growth restriction). Both scenarios are considered clinically important and possibly associated with periodontal disease.

Due to these potential biases and differences in the definitions of periodontal disease and adverse pregnancy outcomes, we did not pool the effect sizes (ORs or RRs) but had to rely on the weaker "vote-counting" method for the observational studies in this review, nor did we assess the quality of all 44 studies.

Implications for Future Research. There is a clear need for methodologically rigorous observational studies in this area (i.e., with clear and consistent definitions of periodontal disease and adverse pregnancy outcomes, sufficiently large sample sizes, and controls for key confounders).

- Because of growing research interest in this topic, we need to develop a more universally accepted *research* definition of and severity criteria for periodontal disease. Most current definitions are based on diagnostic and treatment decisions involving dentition, which may have little or nothing in common with disease aspects that are relevant to the systemic outcomes under study.

- Clinical periodontal measures (PD and CAL) can be analyzed more objectively as continuous variables in association with birth outcomes, as demonstrated by Romero et al.[47] Another option is to categorize patients according to quartiles determined by the distribution of periodontal indicators in a study population. Using the lowest quartile category as a referent, dose-response relationships could be tested to examine if risks of adverse outcomes increase with periodontal disease severity.

- Future studies also need to minimize the effects of the other potential biases discussed above. This is especially true in terms of sample size, which needs to be sufficiently large for assessing the effects of periodontal disease and possible interactions between periodontal disease and other risk factors such as ethnicity, socioeconomic status and smoking.

- Periodontal disease and adverse pregnancy outcomes share several confounders, such as smoking, socioeconomic factors and age. Although most studies attempted to adjust for the confounding factors, it is possible that some residual confounding effects remain. The role of smoking as a major confounder is further obscured by the different classification of smokers as previous smokers, light or heavy smokers, or by reporting years of smoking. It would be beneficial to conduct future studies restricted among non-smokers. In the USA, many studies reported a rather "skewed" patient population that makes interpretation of results problematic; the percentage of African-Americans, for example, varies from 46.2%[54] to 82.68%,[45] making comparisons between studies problematic. It would be advantageous to restrict or separate the analysis on African-American women in certain studies, or to combine subpopulations from several studies to investigate the effect of the socioeconomic factors and race/ethnicity on the association between periodontal disease and adverse pregnancy outcomes.

- As more studies are conducted on this topic, we may be able to pool *original data* (as opposed to meta-analysis by pooling ORs and RRs) from different studies. Such efforts would allow for use of the same definitions for periodontal disease and adverse pregnancy outcomes. With sufficient sample sizes, the pooled original data studies could examine not only if periodontal disease is an independent risk factor, but also if the effect of periodontal disease on adverse pregnancy outcomes are different according to different regions and populations (e.g., ethnic, socioeconomic and maternal smoking status).

Implications for Clinical Practice. Although more methodologically rigorous studies are needed for confirmation of the association between periodontal diseases and adverse pregnancy outcomes, the importance of preventive measures for oral/periodontal health cannot be overstated. Periodontal health is a component of general health. Prevention and treatment of periodontal diseases are important to maintain health.[76, 77]

- Prevention of periodontal disease should start before and independently of pregnancy. Women should be informed on the importance of oral/periodontal health as an integral part of overall health and well-being.

- Pregnant women should be educated on possible impact of periodontal infection on pregnancy outcomes, periodontal prevention and treatment options.[76]

- For pregnant women, proper periodontal examination and treatment, if indicated, may have a beneficial effect on the health of their babies. These recommendations are not different to the recommendations given to the general public, with regards to periodontal disease prevention.

- The primary objectives of therapy for patients with periodontal disease are to halt disease progression and to resolve inflammation. Appropriate therapy for patients with periodontal disease varies with the extent and pattern of attachment loss and therapeutic objectives.[78] Non-surgical periodontal procedures are more economical compared to surgical interventions,[79]and since they are safe and with minimal adverse effects,[19] they should be the treatment of choice for pregnant patients with periodontal inflammation.

- The beneficial effects of scaling and root planing combined with personal oral hygiene in the treatment of periodontitis have been established several years ago.[80] These effects include reduction of clinical inflammation, microbial shifts to a less pathogenic subgingival flora, decreased probing depth and gain of clinical attachment.[78]

Implications for Policy Making. Although more studies, especially randomized controlled trials, are needed to clarify whether or not periodontal treatment has any role in reducing adverse birth outcomes,[81] we feel that there are certain actions that should be taken already:

- Periodontal diseases are preventable and treatable. Regardless of the potential for improving oral health to improve pregnancy outcomes, public health policies should support comprehensive dental services for pregnant or pre-pregnancy women, in particular for high risk (e.g., low socioeconomic status or African-American) women, so that their own oral and general health, as well as their children's health are safeguarded.[82]

- Prevention consists of patient education, at-home personal oral hygiene, and regular professional check-ups and dental cleanings, along with prevention of behaviors such as smoking. These universal recommendations should be the cornerstone of our intervention for pregnant women, starting from childhood, in school.

- Only 23-43% of women received dental care during pregnancy in this country.[83, 84] Pregnant women covered by Medicaid were less likely to obtain a dental visit during pregnancy than women who are privately insured (data from CDC's Pregnancy Risk Assessment Monitoring

System—PRAMS). Three states (UT, LA, and CA) have recently expanded Medicaid dental benefits specifically to pregnant women in anticipation of reduced rates of unfavorable pregnancy outcomes. Such programs of providing dental care consisting mainly of preventive/non-invasive periodontal treatment to low socioeconomic status pregnant women may be beneficial to the health of women and their infants.

CONCLUSION

- There is evidence of an association between periodontal disease and increased risk of preterm birth and low birth weight, especially in economically disadvantaged populations, but potential biases (especially in terms of inconsistent definitions of periodontal disease) and the limited number of randomized controlled trial studies prevent us from offering a clear conclusion.

- There is insufficient evidence to support the provision of periodontal treatment during pregnancy for the purpose of reducing adverse pregnancy outcomes.

- Several randomized controlled trials are underway to test the hypothesis that periodontal treatment can reduce rates of certain adverse pregnancy outcomes. The findings from these trials (or through a meta-analysis) would provide more definitive conclusion.

- More studies are needed to examine potential associations between periodontal disease and increased risk of maternal complications (gestational diabetes mellitus and pre-eclampsia), early pregnancy loss or miscarriage, stillbirth, and very preterm birth (<32 weeks).

GLOSSARY

Confounding variable: A variable that can cause or prevent the outcomes of interest and is associated with the factor under investigation.

Effect modification: A measure of effect changes over the level of another variable.

Gestational diabetes mellitus (GDM): Any degree of glucose intolerance with onset or first recognition during pregnancy.

Intrauterine growth restriction (Small-for-gestational age): Birth weight < 10^{th} percentile for expected gestational age.

Low birth weight: Birth weight < 2,500 g.

Meta-analysis: The statistical procedure for combining data from multiple studies.

Miscarriage: A therapeutic or spontaneous pregnancy loss prior to 20 weeks of gestation or of products of conception < 500 g.

Pre-eclampsia: A blood pressure of ≥140/90 mmHg (i.e., gestational hypertension) with proteinuria of 1+ on dipstick or >0.3 g in a 24-hour urine collection after 20 weeks of gestation.

Preterm birth: Birth before 37 weeks of gestation.

Stillbirth: Fetal death occurs after 20 weeks of gestation.

Systematic review: A summary of the literature that uses explicit methods to perform a thorough literature search and critical appraisal of individual studies to identify the valid and applicable evidence and then uses appropriate techniques to combine these valid studies.

References

1. PAPAPANOU PN. Periodontal diseases: epidemiology. Ann Periodontol 1996;1:1-36.
2. ALBANDAR JM, RAMS TE. Global epidemiology of periodontal diseases: an overview. Periodontol 2000 2002;29:7-10.
3. ALBANDAR JM. Periodontal diseases in North America. Periodontol 2000 2002;29:31-69.
4. OFFENBACHER S, LIEFF S, BOGGESS KA, et al. Maternal periodontitis and prematurity. Part I: Obstetric outcome of prematurity and growth restriction. Ann Periodontol 2001;6:164-74.
5. PIHLSTROM BL, MICHALOWICZ BS, JOHNSON NW. Periodontal diseases. Lancet 2005;366:1809-20.
6. KINANE DF. Causation and pathogenesis of periodontal disease. Periodontol 2000;25:8-20.
7. KORNMAN KS, PAGE RC, TONETTI MS. The host response to the microbial challenge in periodontitis: assembling the players. Periodontol 2000;14:33-53.
8. OFFENBACHER S, KATZ V, FERTIK G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol 1996;67:1103-13.
9. GARCIA RI, HENSHAW MM, KRALL EA. Relationship between periodontal disease and systemic health. Periodontol 2000;25:21-36.
10. CHAMPAGNE CM, MADIANOS PN, LIEFF S, MURTHA AP, BECK JD, OFFENBACHER S. Periodontal medicine: emerging concepts in pregnancy outcomes. J Int Acad Periodontol 2000;2:9-13.
11. PAQUETTE DW. The periodontal infection-systemic disease link: a review of the truth or myth. J Int Acad Periodontol 2002;4:101-9.
12. XIONG X, BUEKENS P, FRASER WD, BECK J, OFFENBACHER S. Periodontal disease and adverse pregnancy outcomes: a systematic review. BJOG 2006;113:135-43.
13. MCCORMICK MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med 1985;312:82-90.
14. SHENNAN AH. Recent developments in obstetrics. BMJ 2003;327:604-8.
15. XIONG X, BUEKENS P, VASTARDIS S, WU T. Periodontal disease as one possible explanation for the Mexican paradox. Med Hypotheses 2006;67:1348-54.
16. MITCHELL-LEWIS D, ENGEBRETSON SP, CHEN J, LAMSTER IB, PAPAPANOU PN. Periodontal infections and pre-term birth: early findings from a cohort of young minority women in New York. Eur J Oral Sci 2001;109:34-9.
17. LOPEZ NJ, SMITH PC, GUTIERREZ J. Periodontal therapy may reduce the risk of preterm low birth weight in women with periodontal disease: a randomized controlled trial. J Periodontol 2002;73:911-24.
18. JEFFCOAT MK, HAUTH JC, GEURS NC, et al. Periodontal disease and preterm birth: results of a pilot intervention study. J Periodontol 2003;74:1214-8.
19. MICHALOWICZ BS, HODGES JS, DIANGELIS AJ, et al. Treatment of periodontal disease and the risk of preterm birth. N Engl J Med 2006;355:1885-94.
20. PETITTI DB. Meta-analysis, decision analysis and cost-effectiveness analysis. New York: Oxford University Press, 1994.
21. DERSIMONIAN R, LAIRD N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
22. DASANAYAKE AP. Poor periodontal health of the pregnant woman as a risk factor for low

birth weight. Ann Periodontol 1998;3:206-12.
23. SEMBENE M, MOREAU JC, MBAYE MM, et al. [Periodontal infection in pregnant women and low birth weight babies]. Odontostomatol Trop 2000;23:19-22.
24. LOURO PM, FIORI HH, FILHO PL, STEIBEL J, FIORI RM. [Periodontal disease in pregnancy and low birth weight]. J Pediatr (Rio J) 2001;77:23-8.
25. DAVENPORT ES, WILLIAMS CE, STERNE JA, MURAD S, SIVAPATHASUNDRAM V, CURTIS MA. Maternal periodontal disease and preterm low birthweight: case-control study. J Dent Res 2002;81:313-8.
26. FRASER WD, BIGIRIMANA PC, BEAUDRY L, XIONG X, CHANDAD F. Is periodontal disease a risk factor for spontaneous preterm delivery? A case-control study (unpublished data). 2004.
27. MOKEEM SA, MOLLA GN, AL-JEWAIR TS. The prevalence and relationship between periodontal disease and pre-term low birth weight infants at King Khalid University Hospital in Riyadh, Saudi Arabia. J Contemp Dent Pract 2004;5:40-56.
28. GOEPFERT AR, JEFFCOAT MK, ANDREWS WW, et al. Periodontal disease and upper genital tract inflammation in early spontaneous preterm birth. Obstet Gynecol 2004;104:777-83.
29. RADNAI M, GORZO I, NAGY E, URBAN E, NOVAK T, PAL A. A possible association between preterm birth and early periodontitis. A pilot study. J Clin Periodontol 2004;31:736-41.
30. CANAKCI V, CANAKCI CF, CANAKCI H, et al. Periodontal disease as a risk factor for pre-eclampsia: A case control study. Aust N Z J Obstet Gynaecol 2004;44:568-73.
31. MOORE S, RANDHAWA M, IDE M. A case-control study to investigate an association between adverse pregnancy outcome and periodontal disease. J Clin Periodontol 2005;32:1-5.
32. BUDUNELI N, BAYLAS H, BUDUNELI E, TURKOGLU O, KOSE T, DAHLEN G. Periodontal infections and pre-term low birth weight: a case-control study. J Clin Periodontol 2005;32:174-81.
33. JARJOURA K, DEVINE PC, PEREZ-DELBOY A, HERRERA-ABREU M, D'ALTON M, PAPAPANOU PN. Markers of periodontal infection and preterm birth. Am J Obstet Gynecol 2005;192:513-9.
34. OETTINGER-BARAK O, BARAK S, OHEL G, et al. Severe pregnancy complication (preeclampsia) is associated with greater periodontal destruction. J Periodontol 2005;76:134-7.
35. NOACK B, KLINGENBERG J, WEIGELT J, HOFFMANN T. Periodontal status and preterm low birth weight: a case control study. J Periodontal Res 2005;40:339-45.
36. CRUZ SS, COSTA MDA C, GOMES FILHO IS, VIANNA MI, SANTOS CT. [Maternal periodontal disease as a factor associated with low birth weight]. Rev Saude Publica 2005;39:782-7.
37. MOLITERNO LF, MONTEIRO B, FIGUEREDO CM, FISCHER RG. Association between periodontitis and low birth weight: a case-control study. J Clin Periodontol 2005;32:886-90.
38. LUNARDELLI AN, PERES MA. Is there an association between periodontal disease, prematurity and low birth weight? A population-based study. J Clin Periodontol 2005;32:938-46.
39. SKULDBOL T, JOHANSEN KH, DAHLEN G, STOLTZE K, HOLMSTRUP P. Is pre-term labour

associated with periodontitis in a Danish maternity ward? J Clin Periodontol 2006;33:177-83.
40. HUJOEL PP, LYDON-ROCHELLE M, ROBERTSON PB, DEL AGUILA MA. Cessation of periodontal care during pregnancy: effect on infant birthweight. Eur J Oral Sci 2006;114:2-7.
41. CASTALDI JL, BERTIN MS, GIMENEZ F, LEDE R. [Periodontal disease: Is it a risk factor for premature labor, low birth weight or preeclampsia?]. Rev Panam Salud Publica 2006;19:253-8.
42. BOSNJAK A, RELJA T, VUCICEVIC-BORAS V, PLASAJ H, PLANCAK D. Pre-term delivery and periodontal disease: a case-control study from Croatia. J Clin Periodontol 2006.
43. CONTRERAS A, HERRERA JA, SOTO JE, ARCE RM, JARAMILLO A, BOTERO JE. Periodontitis is associated with preeclampsia in pregnant women. J Periodontol 2006;77:182-8.
44. XIONG X, BUEKENS P, VASTARDIS S, PRIDJIAN G. Periodontal disease and gestational diabetes mellitus. Am J Obstet Gynecol 2006;195:1086-9.
45. JEFFCOAT MK, GEURS NC, REDDY MS, CLIVER SP, GOLDENERG RL, HAUTH JC. Periodontal infection and preterm birth: results of a prospective study. J Am Dent Assoc 2001;132:875-80.
46. LOPEZ NJ, SMITH PC, GUTIERREZ J. Higher risk of preterm birth and low birth weight in women with periodontal disease. J Dent Res 2002;81:58-63.
47. ROMERO BC, CHIQUITO CS, ELEJALDE LE, BERNARDONI CB. Relationship between periodontal disease in pregnant women and the nutritional condition of their newborns. J Periodontol 2002;73:1177-83.
48. BOGGESS KA, LIEFF S, MURTHA AP, MOSS K, BECK J, OFFENBACHER S. Maternal periodontal disease is associated with an increased risk for preeclampsia. Obstet Gynecol 2003;101:227-31.
49. MOORE S, IDE M, COWARD PY, et al. A prospective study to investigate the relationship between periodontal disease and adverse pregnancy outcome. Br Dent J 2004;197:251-8; discussion 247.
50. HOLBROOK WP, OSKARSDOTTIR A, FRIDJONSSON T, EINARSSON H, HAUKSSON A, GEIRSSON RT. No link between low-grade periodontal disease and preterm birth: a pilot study in a healthy Caucasian population. Acta Odontol Scand 2004;62:177-9.
51. DORTBUDAK O, EBERHARDT R, ULM M, PERSSON GR. Periodontitis, a marker of risk in pregnancy for preterm birth. J Clin Periodontol 2005;32:45-52.
52. RAJAPAKSE PS, NAGARATHNE M, CHANDRASEKRA KB, DASANAYAKE AP. Periodontal Disease and Prematurity among Non-smoking Sri Lankan Women. J Dent Res 2005;84:274-7.
53. MOREU G, TELLEZ L, GONZALEZ-JARANAY M. Relationship between maternal periodontal disease and low-birth-weight pre-term infants. J Clin Periodontol 2005;32:622-7.
54. OFFENBACHER S, BOGGESS KA, MURTHA AP, et al. Progressive periodontal disease and risk of very preterm delivery. Obstet Gynecol 2006;107:29-36.
55. BOGGESS KA, BECK JD, MURTHA AP, MOSS K, OFFENBACHER S. Maternal periodontal disease in early pregnancy and risk for a small-for-gestational-age infant. Am J Obstet Gynecol 2006;194:1316-22.
56. FARRELL S, IDE M, WILSON RF. The relationship between maternal periodontitis, adverse

pregnancy outcome and miscarriage in never smokers. J Clin Periodontol 2006;33:115-20.
57. SADATMANSOURI S, SEDIGHPOOR N, AGHALOO M. Effects of periodontal treatment phase I on birth term and birth weight. J Indian Soc Pedod Prev Dent 2006;24:23-6.
58. RADNAI M, GORZO I, URBAN E, ELLER J, NOVAK T, PAL A. Possible association between mother's periodontal status and preterm delivery. J Clin Periodontol 2006;33:791-6.
59. WOOD S, FRYDMAN A, COX S, et al. Periodontal disease and spontaneous preterm birth: a case control study. BMC Pregnancy Childbirth 2006;6:24.
60. JEFFCOAT MK, GEURS NC, REDDY MS, GOLDENBERG RL, HAUTH JC. Current evidence regarding periodontal disease as a risk factor in preterm birth. Ann Periodontol 2001;6:183-8.
61. MINKOFF H. Prematurity: infection as an etiologic factor. Obstet Gynecol 1983;62:137-44.
62. GIBBS RS, ROMERO R, HILLIER SL, ESCHENBACH DA, SWEET RL. A review of premature birth and subclinical infection. Am J Obstet Gynecol 1992;166:1515-28.
63. GIBBS RS. The relationship between infections and adverse pregnancy outcomes: an overview. Ann Periodontol 2001;6:153-63.
64. REDMAN CW, SACKS GP, SARGENT IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol 1999;180:499-506.
65. VON DADELSZEN P, MAGEE LA. Could an infectious trigger explain the differential maternal response to the shared placental pathology of preeclampsia and normotensive intrauterine growth restriction? Acta Obstet Gynecol Scand 2002;81:642-8.
66. SCONYERS JR, CRAWFORD JJ, MORIARTY JD. Relationship of bacteremia to toothbrushing in patients with periodontitis. J Am Dent Assoc 1973;87:616-22.
67. OFFENBACHER S, JARED HL, O'REILLY PG, et al. Potential pathogenic mechanisms of periodontitis associated pregnancy complications. Ann Periodontol 1998;3:233-50.
68. RAMFJORD SP. Indices for prevalence and incidence of periodontal disease. J Periodontol 1959;30:51-59.
69. LOEE H, SILNESS J. Periodontal Disease in Pregnancy. I. Prevalence and Severity. Acta Odontol Scand 1963;21:533-51.
70. AINAMO J, BARMES D, BEAGRIE G, CUTRESS T, MARTIN J, SARDO-INFIRRI J. Development of the World Health Organization (WHO) community periodontal index of treatment needs (CPITN). Int Dent J 1982;32:281-91.
71. CARLOS JP, WOLFE MD, KINGMAN A. The extent and severity index: a simple method for use in epidemiologic studies of periodontal disease. J Clin Periodontol 1986;13:500-5.
72. BAELUM V, PAPAPANOU PN. CPITN and the epidemiology of periodontal disease. Community Dent Oral Epidemiol 1996;24:367-8.
73. HUJOEL PP, DRANGSHOLT M, SPIEKERMAN C, DEROUEN TA. Periodontitis-systemic disease associations in the presence of smoking--causal or coincidental? Periodontol 2000 2002;30:51-60.
74. KRAMER MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ 1987;65:663-737.
75. KRAMER MS. Intrauterine growth and gestational duration determinants. Pediatrics 1987;80:502-11.
76. American Academy of Periodontology statement regarding periodontal management of the pregnant patient. J Periodontol 2004;75:495.

77. Parameter on systemic conditions affected by periodontal diseases. American Academy of Periodontology. J Periodontol 2000;71:880-3.
78. Treatment of plaque-induced gingivitis, chronic periodontitis, and other clinical conditions. J Periodontol 2001;72:1790-800.
79. BRAEGGER U. Cost-benefit, cost-effectiveness and cost-utility analyses of periodontitis prevention. J Clin Periodontol 2005;32 Suppl 6:301-13.
80. GARRETT JS. Effects of nonsurgical periodontal therapy on periodontitis in humans. A review. J Clin Periodontol 1983;10:515-23.
81. GOLDENBERG RL, CULHANE JF. Preterm birth and periodontal disease. N Engl J Med 2006;355:1925-7.
82. BOGGESS KA, EDELSTEIN BL. Oral Health in Women During Preconception and Pregnancy: Implications for Birth Outcomes and Infant Oral Health. Matern Child Health J 2006.
83. GAFFIELD ML, GILBERT BJ, MALVITZ DM, ROMAGUERA R. Oral health during pregnancy: an analysis of information collected by the pregnancy risk assessment monitoring system. J Am Dent Assoc 2001;132:1009-16.
84. MANGSKAU KA, ARRINDELL B. Pregnancy and oral health: utilization of the oral health care system by pregnant women in North Dakota. Northwest Dent 1996;75:23-8.

Table 1. Periodontal Disease and Adverse Pregnancy Outcomes: Case-Control Studies

Authors Published year Country (Reference)	Sample size	Characteristics of population	Definitions of periodontal disease	Outcomes & OR or RR* (95% CI)	Confounders being controlled	Conclusions
Offenbacher S et al 1996 USA[8]	Cases: 93 Controls: 31	Black: 59% White: 30% Others: 11%	Extent 3:60: (60% sites with CAL**≥ 3mm)	PLBW[#]: aOR: 7.5 (1.95-28.8)	Yes	Periodontal disease is a risk factor for PLBW.
Dasanayake AP et al 1998 Thailand[22]	Cases: 50 Controls: 50	Low social class: Husband: 85% cases 67% controls Father: 85% cases 78% controls	DMFT and CPITN[$]: Number of healthy sextants	LBW[&]: aOR: 0.3 (0.12-0.72) aOR: 1.1 (0.97-1.4)	Yes	Periodontal disease is a potential independent risk factor for LBW.
Sembene M et al 2000 Senegal[23]	Cases: 26 Controls: 87		CPITN score: ≤ 1 1-1.99 2-2.99 ≥ 3	LBW: OR:† 1.00 (ref.) 0.00 3.83 53.7 Overall OR:† 2.76 (0.69-12.75)	No	Periodontal disease is a potential risk factor for LBW.
Louro PM et al 2001 Brazil[24]	Cases: 13 Controls: 13	Low family income: 54%	Extension and severity index (Carlos, et al.[71])	LBW: aOR: 7.2 (0.4-125.4)	Yes	Periodontal disease may be a risk factor for LBW.
Davenport ES et al 2002 UK[25]	Cases: 236 Controls: 507	Bengali: 52.5% White or Irish: 30.7% Others: 16.8%	Mean PD[@] (mm)	PLBW: aOR: 0.78 (0.64-0.99)	Yes	There is no evidence for an association between periodontal disease and PLBW.
Fraser W et al 2003 Canada [26] (Unpublished data)	Cases: 147 Controls: 303	Caucasian >93%	40% sites with PD ≥4 mm	PTB[√]: aOR: 2.54 (0.65-9.89)	Yes	Periodontal disease is not a significant risk factor for PTB.
Mokeem SA	Cases: 30	Medium or high	Mean CPITN	PLBW:	Yes	There is a correlation

et al 2004 Saudi Arabia[27]	Controls: 60	social class: 83%		aOR: 4.21 (1.99-8.93)		between periodontal disease and PLBW.
Goepfert AR et al 2004 USA[28]	Cases: 59 Controls: 44	African-American: 63%	Severe periodontal disease: > 5 mm in any one sextant	Spontaneous PTB: aOR: 3.4 (1.5-7.7)	Yes	Women with early spontaneous preterm birth are more likely to have severe periodontal disease.
Radnai M et al 2004 Hungary[29]	Cases: 41 Controls: 44		Periodontitis: ≥ 1 sites with PD ≥ 4 mm and ≥ 50% teeth with BOP[§]	PTB and LBW: OR: 5.46 (1.72-17.3)	No	Early localized periodontitis can be regarded as an important risk factor for PTB.
Canakci V et al 2004 Turkey[30]	Cases: 41 Controls: 41		≥ 4 teeth with ≥ 1 sites with PD ≥ 4 mm that bled on probing and with a CAL ≥ 3 mm at the same site	Pre-eclampsia: aOR: 3.47 (1.07-11.95)	Yes	Periodontal disease is associated with an increased risk for the development of pre-eclampsia.
Moore S et al 2005 UK[31]	Cases: 61 Controls: 93	White: 47.4% Black: 42.9% Other; 9.7%	Number of sites with PD ≥ 5 mm	PTB: 2% in cases vs. 4% in controls (p=0.016)	No	There is no association between the severity of periodontal disease and pregnancy outcome.
Buduneli N et al 2005 Turkey[32]	Cases: 53 Controls: 128		Number of sites with BOP Number of sites with PD ≥ 4 mm	PLBW: 42.6% in cases vs. 42.3% in controls (p=0.939) 7.6% in cases vs. 9.0% in controls (p=0.445)	No	There are no differences in dental and periodontal parameters between the cases and the controls.
Jarjoura K et al 2005 USA[33]	Cases: 83 Controls: 120	Hispanic: 61.1% Black: 15.3% White: 22.2%	Periodontitis: ≥ 5 sites with CAL ≥ 3mm	PTB: aOR: 2.75 (1.01-7.54) LBW: aOR: 1.99 (0.73-5.45)	Yes	Periodontitis is independently associated with PTB and LBW.
Oettinger-Barak O et al	Cases: 15		Mean PD and CAL	Pre-eclampsia:		There is a possible association between

2005 Israel[34]	Controls: 15			Mean CAL: 3.33 mm in cases vs. 2.30 mm in controls		periodontal inflammation and pre-eclampsia.
Noack B et al 2005 Germany[35]	Cases: 59 Controls: 42		Mean % sites with CAL ≥ 3 mm	PLBW: aOR: 0.73 (0.13-4.19)	Yes	Periodontitis is not a risk factor for PLBW.
Cruz SS et al 2005 Brasil[36]	Cases: 102 Controls: 200	Family income < minimum wages: 60.3%	≥ 4 teeth with CAL ≥ 4 mm	LBW: OR: 2.15 (1.32-3.48) aOR: 3.98 (1.58-10.10) in schooling ≤ 4 years	Yes	Periodontal disease is a possible risk factor for LBW.
Moliterno LFM et al 2005 Brazil[37]	Cases: 76 Controls: 75		≥ 4 sites with PD ≥ 4 mm and CAL ≥ 3 mm	LBW: aOR: 3.48 (1.17-10.36)	Yes	Periodontitis is a risk factor for LBW.
Lunardelli AN et al 2005 Brazil[38]	449 women: LBW: 26 PTB: 32	White: 92.6% Black: 7.4%	≥ 1 site with PD or the presence of PD ≥ 4 sites	LBW: No association PTB: aOR: 2.6 (1.0-6.9)	Yes	Periodontal disease is not associated with LBW or PTB
Skuldbol T et al 2006 Denmark[39]	Cases: 21 Controls: 33		PD ≥ 4 mm (% sites)	PTB: 3.83 in cases vs. 3.05 in controls (p > 0.05)	No	Periodontitis is not associated with PTB.
Hujoel PP et al 2006 USA[40]	Cases: 793 Controls: 3172	Caucasian: >80.2%	Cessation of periodontal care during pregnancy	LBW: aOR: 0.96 (0.60-1.52)	Yes	Periodontal care patterns in pregnancy are unrelated to LBW.
Castaldi JL et al 2006 Argentina[41]	1562 women: 149 PTB 161 LBW 157 Preeclampsia		≥ 4 teeth with PD or CAL ≥ 3 mm	PTB: aOR: 1.06 (0.74-1.50) LBW: aOR: 1.05 (0.74-1.47) Pre-eclampsia: aOR: 0.99 (0.70-1.40)	Yes	No association is found between periodontal disease and PTB, LBW, or pre-eclampsia.
Bosnjak A et al	Cases: 17	Primiparous women	Extent 4:60: (60% sites with	PTB: aOR: 8.13 (2.73-45.9)	Yes	Periodontal disease represents a

2006 Croatia[42]	Controls: 64		CAL ≥ 4 mm			significant risk factor for PTB.
Contreras A et al 2006 Colombia[43]	Cases: 130 Controls: 243	Mixed race: 80.7% Black: 15% Native: 4.3%	≥ 2 sites with PD ≥ 4 mm, and CAL ≥ 4 mm and bleeding on probing	Preeclampsia: OR: 3.0 (1.91-4.87)	No	Chronic periodontal disease is significantly associated with pre-eclampsia.
Xiong X et al 2006 USA[44]	Cases : 11 Controls :245	White: 75.9% Black: 16.8% Other: 7.3%	At least 1 site with CAL or PD ≥ 4 mm	Gestational diabetes: aOR: 9.11 (1.11-74.9)	Yes	There may be an association between periodontal disease and GDM.
Radnai M et al 2006 Hungary[58]	Cases: 77 Control: 84		≥4 mm PD at least at one site and BOP at ≥50% of the teeth	PTB: aOR: 3.32 (1.64-6.69)	Yes	Periodontitis of pregnant women could lead to PTB.
Wood S et al 2006 Canada[59]	Cases: 50 Controls: 101		Proportion of sites with CAL ≥ 3 mm.	PTB: aOR: 0.56 (0.13-2.37)	Yes	Periodontal disease is not associated with spontaneous preterm birth.

OR or RR: odds ratio or risk ratio; aOR or aRR: OR or RR was adjusting for confounders; ** CAL: Clinical attachment loss;
PLBW: preterm low birth weight; $ DMFT: Decayed, Missing, and Filled Teeth; CPITN: Community Periodontal Index of Treatment Needs;
& LBW: Low birth weight; †, computed from data; @ PD: probing depth; √ PTB: preterm birth; § BOP: bleeding on probing.

Table 2. Periodontal Disease and Adverse Pregnancy Outcomes: Cohort Studies

Authors Published year Country (Reference)	Sample size	Characteristics of population	Definitions of periodontal disease	Outcomes & OR or RR* (95% CI)	Confounders being controlled	Conclusions
Jeffcoat MK et al 2001 USA[45]	1,313 pregnancies	African-American: 82.68% Caucasian: 17.32%	Periodontitis: ≥ 3 sites with CAL** ≥ 3mm ≥ 90 sites with CAL ≥ 3mm	PTB[√] (< 37 weeks): aOR: 4.45 (2.16-9.18) PTB (< 35 wks): aOR: 5.28 (2.05-13.6) PTB (< 32 wks): aOR: 7.07 (1.70-27.40)	Yes	Periodontal disease is an independent risk factor for PTB.
Offenbacher S et al 2001 USA[4]	Healthy: 201 cases; Mild periodontal disease: 566 cases; Moderate-severe periodontal disease: 45 cases	50.1% Black 44.5% White 5.4% Other Overall preterm birth rate: 23.1%	Mild: PD[@] >3mm or CAL>2mm Moderate-severe: (≥ 4 sites with PD ≥ 5 mm and ≥ 4 sites with CAL ≥ 2 mm)	PTB: aOR: 1.23 (0.89-1.70) aOR: 2.12 (1.34-3.35)	Yes	Periodontal disease is a significant risk factor for PTB, SGA[‡] and LBW[&].
Lopez NJ et al 2002 Chile[46]	Periodontal disease group: 233 Control: 406	Low socioeconomic status	≥ 4 teeth with ≥ 1 sites with PD ≥ 4mm and with CAL ≥ 3mm	PLBW[#]: aRR: 3.5 (1.5-7.9) PTB: aRR: 2.9 (1.0-8.1) LBW: aRR: 3.6 (1.07-12.2)	Yes.	Periodontal disease is an independent risk factor for PTB and LBW.
Romero BC et al 2002 Venezuela[47]	69 women	N/A	Russell's index: 1: health (n=13) 2: simple gingivitis (n=17) 3: initial periodontitis (n=33) 4: established periodontitis (n=6)	Birth weight or gestational age: Correlation analysis: more severe periodontal disease and lower birth weight (r=-0.49; p< 0.01) and decreasing gestational age (r = -0.59; P < 0.01).	N/A	Periodontal disease could be a clinically significant risk factor for preterm deliveries and low birth weight.
Boggess KA et al 2003	Mild periodontal disease: 496	White: 47% Black: 47% Other: 5%	Severe periodontal disease: ≥ 15 sites with PD ≥ 4 mm	Pre-eclampsia: aOR: 2.4 (1.1-5.3)	Yes	Periodontal disease is associated with an increased risk of pre-

USA[48]	Severe periodontal disease: 125 Control: 229	Married: 51% Food stamp use: 22%				eclampsia
Moore S et al 2004 UK[49]	3738 pregnancies	White: 62.3% Black: 28.2% Other: 9.5%	% of sites with BOP[§] Number of sites with PD ≥ 4 or 5 mm	PTB or LBW: No difference between women with PTB or LBW and without PTB or LBW Miscarriage or stillbirth: aOR: 2.54 (1.20-5.39)	Yes	There is no association between either preterm birth or LBW and periodontal disease.
Holbrook WP et al 2004 Iceland[50]	96 pregnancies	Caucasian: 100%	PD> 4 mm, putative periodontal pathogens, yeasts from gingival culture.	None of the parameters measured was more prevalent in the women that subsequently gave birth to PTB	No	There is no link between low-grade periodontal disease and PTB in a healthy Caucasian population.
Dortbudak O et al 2005 Austria[51]	36 women at risk for pregnancy complications		PD ≥ 5 mm and gingival inflammation and presence of pathogens	PTB or LBW: OR: 20.0 (2.0-201.7)	No	Periodontitis can induce a primary host response in the chorioamnion leading to PTB.
Rajapakse PS et al 2005 Sri Lanka[52]	227 non-smoking pregnancies	Living in rural areas with annual household income<$400	Mean PD, plaque scores and bleeding scores > median value in the total cohort	PLBW: aOR: 1.9 (0.7-5.4)	Yes	Periodontal disease is not a significant risk factor for PTB
Moreu G et al 2005 Spain[53]	96 women		Percentage of sites with PD > 3 mm	PTB: No association LBW: There is an association between the proportion of sites with PD >3 mm and LBW	Yes	Periodontal disease is a risk factor for LBW but not for PTB.
Offenbacher S et al 2006 USA[54]	Healthy: 285 cases; Mild periodontal disease: 588	46.2 % Black 47.7% White 6.1% Other	Moderate-severe periodontal disease: (≥ 15 sites with PD ≥ 4 mm)	PTB: aRR: 2.00 (1.20-3.20)	Yes	Periodontal disease is a significant risk factor for PTB and very PTB.

	cases; Moderate-severe periodontal disease: 147 cases		Progressive periodontal disease: (≥ 4 sites with increased PD ≥ 2 mm between ante- and post-partum visits)	Very PTB (<32 weeks): aRR: 2.4 (1.1-5.2)		
Boggess, KA et al 2006 USA[55]	Healthy: 284 cases; Mild periodontal disease: 588 cases; Moderate-severe periodontal disease: 145 cases	50.1% Black 44.5% White 5.4% Other 48.7% unmarried 52.5% uninsured	Moderate-severe periodontal disease: (≥ 15 sites with PD ≥ 4 mm)	SGA: aRR: 2.30 (1.10-4.50)	Yes	Periodontal disease is associated with delivery of an SGA infant.
Farrell S et al 2006 UK[56]	1793 women	Non-smokers 59.4% White 29.9% Black 10.7% Other	Increased mean PD (mesial sites)	Miscarriage/stillbirth: aOR: 3.84 (1.68-8.75) PTB or LBW: No association	Yes	Periodontal disease is associated with late miscarriage but not with PTB or LBW.

N/A, not available; * OR or RR: odds ratio or risk ratio; aOR or aRR: OR or RR was adjusting for confounders;
** CAL: Clinical attachment loss; √ PTB: preterm birth; ‡ SGA: small-for-gestational age; # PLBW: preterm low birth weight;
& LBW: Low birth weight; @ PD: probing depth; § BOP: bleeding on probing.

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Table 3. Periodontal Disease and Adverse Pregnancy Outcomes: Controlled Trials

Authors Published year Country (Reference)	Sample size	Characteristics of population	Definitions of periodontal disease	Outcomes & OR or RR* (95% CI)	Conclusions
Mitchell-Lewis et al 2001 USA[16]	Oral prophylaxis group: 74 Control group: 90	60% African-American, 39% Hispanic, all of low socioeconomic status	Oral prophylaxis group was enrolled during pregnancy and received oral intervention. Control group is recruited postpartum	PLBW[#]: 13.5% in oral prophylaxis group, 18.9% in control group, RR: 0.72 (0.4-1.47)†	There was a 28% reduction in PLBW in the periodontally treated group, but it was not statistically significant.
Lopez NJ et al 2002 Chile[17]	Periodontal disease treatment group: 200 Non-treatment group: 200	Low socioeconomic status	≥ 4 teeth with ≥ 1 sites with PD[@] ≥ 4mm and with CAL[**] ≥ 3mm	PLBW: RR: 0.18 (0.05-0.6)† PTB[√]: RR: 0.19 (0.04-0.85)† LBW[$]: RR: 0.16 (0.02-1.33)†	Periodontal disease is an independent risk factor for PLBW.
Jeffcoat MK et al 2003 USA[18]	Group 1: prophylaxis plus placebo capsule, n= 123; Group 2: Scaling and root planing (SRP) plus placebo capsule, n= 123; Group 3: SRP and metronidazole capsule (250mg for 1 week), n= 120	African- American: 85% Married: 13.4%	> 3 sites with CAL≥ 3 mm	PTB[√] < 37 weeks: RR: 0.5 (0.2-1.3) PTB < 35 weeks: RR: 0.2 (0.02-1.4)	Performing scaling and root planning in pregnant women with periodontitis may reduce PTB. Metronidazole therapy did not improve pregnancy outcome.
Sadatmansouri S et al 2006 Iran[57]	Periodontal treatment group: scaling, root planning & 0.2% chlorhexidine mouth rinse for one week: 15 Controls: 15		All women with moderate or advanced periodontitis	PLBW: 4 cases (26.7%) in controls vs. 0 (0%) in treatment group (p <0.05)	Periodontal therapy results in a reduction in PLBW.
Michalowicz BS et al 2006 USA[19]	Periodontal disease treatment group: 413 Control group: 410	White: 28.6% Black: 45.2% Hispanic: 42.5%	≥ 4 teeth with PD ≥ 4 mm and CAL≥ 2 mm and BOP ≥ 35%	PTB: RR: 0.93 (0.63-1.37) LBW: RR: 0.92 (0.61-1.39)† SGA: RR: 1.04 (0.68-1.58)	Treatment of periodontitis in pregnant women does not significantly reduce rates of PTB, LBW, or SGA.

OR or RR: odds ratio or risk ratio; aOR or aRR: OR or RR was adjusting for confounders; # PLBW: preterm low birth weight;
†, computed from data; @ PD: probing depth; ** CAL: Clinical attachment loss; √ PTB: preterm birth; $LBW: low birth weight.

Table 4: Periodontal Disease and Adverse Pregnancy Outcomes: A Summary of Evidence

Outcomes	Studies show 'positive' effect			Studies show 'no' effect		
	No.	Studies	Effect sizes*	No.	Studies	Effect sizes*
Preterm low birth weight	6	2 case-control studies (USA,[8] Saudi Arabia[27]) 1 cohort study (Chile[46]) 3 trials (USA,[16] Chile,[17] Iran[57])	Case-control studies: 4.21-7.5 Cohort study: 3.5 Trials: 0.18 -0.72†	4	3 case-control studies (UK,[25] Turkey,[32] Germany[35]) 1 cohort study (Sri Lanka[52])	Case-control study: 0.78 Cohort study: 1.9
Preterm birth	12	5 case-control studies (USA,[28] Hungary,[29] USA,[33] Croatia,[42] Hungary[58]) 5 cohort studies (USA,[45] USA,[4] Chile,[46] Austria,[51] USA[54]) 2 trials (Chile,[17] USA[18])	Case-control studies: 3.5-5.46 Cohort studies: 2.12-20.0 Trials: 0.72†-0.93	11	6 case-control studies (Canada,[26] UK,[31] Brazil,[38] Denmark,[39] Argentina,[41] Canada[59]) 4 cohort studies (UK,[49] Iceland,[50] Spain,[53] UK[56]) 1 trial (USA[19])	Case-control study: 1.06-2.54 Trial: 0.93
Low birth weight	10	6 case-control studies (Thailand,[22] Senegal,[23] Brazil[24], USA,[33] Brazil,[36] Brazil[37]) 3 cohort studies (USA,[4] Chile,[46] Spain[53]) 1 trial (Chile[17])	Case-control studies: 1.1-7.2 Cohort studies: 3.6 Trial 0.16†	5	2 case-control studies (Brazil,[38] Argentina[41]) 2 cohort studies (UK,[49] UK[56]) Trial (USA[19])	Case-control study: 1.05 Trial: 0.92†
Pre-eclampsia	4	3 case-control studies (Turkey,[30] Israel,[34] Colombia[43]) 1 cohort study (USA[48])	Case-control study: 3.0-3.47 Cohort study: 2.4	1	1 case-control study (Argentina[41])	Case-control study: 0.99
Miscarriage or stillbirth	2	2 cohort studies (UK,[49] UK[56])	Cohort studies: 2.54-3.84			
Intrauterine growth restriction	1	1 cohort study (USA[55])	Cohort study: 2.30	1	1 trial (USA[19])	Trial: 1.04†
Gestational diabetes mellitus	1	1 case-control study (USA[44])	Case-control study: 9.11			

Not all studies provided the effect sizes (i.e., OR, RR).

† For the trial, effect sizes < 1 indicating a reduction in adverse outcomes by the intervention

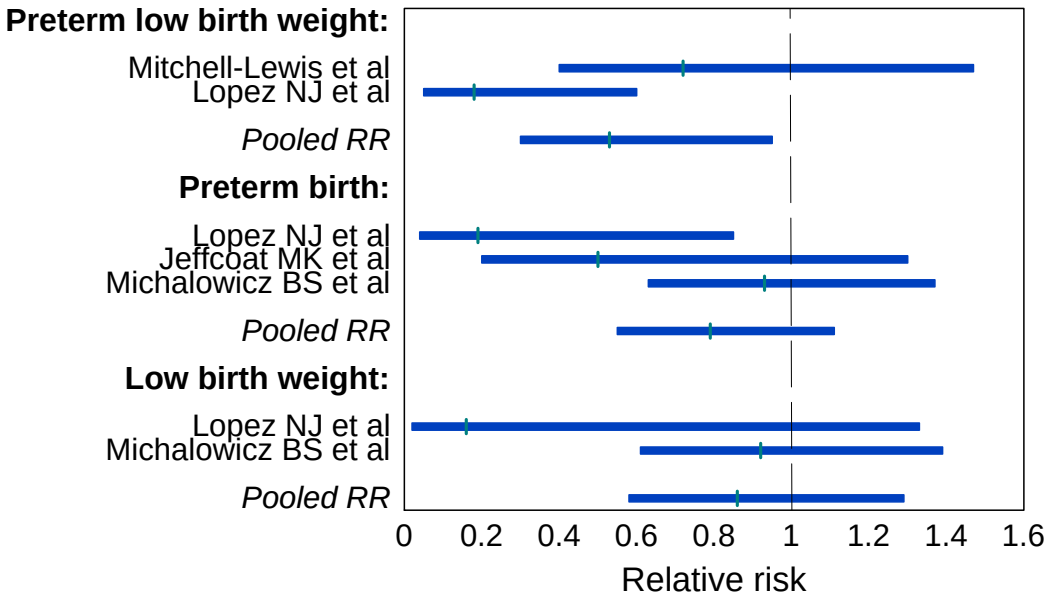

Figure 2: Periodontal disease and birth outcomes: A meta-analysis of clinical trials